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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,154	09/29/2003	John Landers	M0656.70098US00	7775

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EXAMINER	
SALMON, KATHERINE D	

ART UNIT	PAPER NUMBER
1634	

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02/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,154	LANDERS ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *149-166* is/are pending in the application.

4a) Of the above claim(s) *161-164* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *149-160, 165-166* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04, 6/04, 9/03, 10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filled 11/13/2007.

2. Currently Claims 1-48 have been cancelled. Claims 149-166 are pending. Claims 161-164 are withdrawn as being drawn to a nonelected invention.

3. The following rejections to Claims 149-160 and 165-166 are reiterated or newly applied. Response to arguments follows. It is noted that the Double patenting rejection for Claims 149-160 is newly applied.

4. This action is NONFINAL.

Withdrawn Rejections

5. The rejections of Claims 17-21, 25, and 27 under USC 35 112/second paragraph is moot based on the cancellation of the claims.

6. The rejections of Claims 1-5, 8-11, 17-31, 35-36, 38-41, 47-56, 140, 148 under USC 35 102(b) and USC 103(a) is moot based on the cancellation of the claims.

Information Disclosure Statement

7. The information disclosure statement (IDS) submitted on 8/30/2006, 11/29/2004, 1/26/2007, and 8/30/2006. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. **Claims 149-153 and 155-159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) and Cheung et al. (Proceedings National Academy Science 1996 Vol 93 p. 14676)**

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification producing RCG (Column 4 lines 10-20). Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30).

With regard to Claim 149, Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (Column 5 lines 24-25). Shuber et al. teaches a method in which genomic DNA is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 7 paragraph 79 of instant specification). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Shuber et al. teaches a method of detecting the presence or absence of the allele (a SNP) (Column 11 lines 25-30).

Shuber et al. teaches a method incubating RCG (amplified target DNA) with a mixture of allele specific oligonucleotides (ASOs) (Column 4 lines 43-47). Shuber et al. teaches method of detecting the hybridization of the ASO with the RCG wherein the detection of the hybridization indicates if there is a mutation (characterize the genomic sample) (Column 6 lines 5-10 and column 7 lines 25-35).

Shuber et al. teaches using ASO probes to detect the presence or absence of an allele (abstract). Therefore Shuber et al. teaches using SNP ASOs wherein 50% of the time they are in the RCG (the allele is present).

With regard to Claims 155-156, Shuber et al. teaches a method in which the ASO probes can be from 16-25 nucleotides in length (about 10 to about 50 and about 10 to about 25) (Column 4 lines 49-50).

Shuber et al., however, does not teach immobilization of the SNP-ASO probes onto a surface. Shuber et al. teaches genomic DNA is fragmented by PCR amplification to produce a RCG (Column 4 lines 10-20), but does not teach that the production is by using a randomly primed PCR.

With regard to Claim 149, Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

With regard to Claim 149, Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification). Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification). Cheung et al. teaches that arbitrary portions of the DNA sequences are amplified by this method (p. 14676 2nd column 1st paragraph). Therefore Cheung et al. teaches preparing a randomly primed PCR-derived reduced complexity genome with at least one primer. Cheung et al. teaches the amplified fragments of DNA (RCG) are about 500 bp in length (p. 14676 2nd column 1st paragraph); therefore this fragment would contain less than 20% of the genomic material present in the whole genome.

With regard to Claims 150-152, Cheung et al. teaches that the RCG would be about 500 bp in length (p. 14676 2nd column 1st paragraph). The human genome is

about 3 X 10^9 bp in length (p. 14676 2nd column 1st paragraph). Therefore the 500 bp RCG would represent less than 0.05% of the whole genome.

With regard to Claim 153, Cheung et al. teaches that the PCR reaction uses a DOP primer (p. 14676 2nd column DOP amplification).

With regard to Claims 157-159, no patentable weight is given to "identify a loss of heterozygosity in the tumor" as any method for determining the presence or absence of a SNP allele would be used in a method to identify a loss of heterozygoisty in a tumor.

With regard to Claims 158, Cheung et al. teaches that the RCG would be about 500 bp in length (p. 14676 2nd column 1st paragraph). The human genome is about 3 X 10^9 bp in length (p. 14676 2nd column 1st paragraph). Therefore the 500 bp RCG would represent less than 5% of the whole genome.

With regard to Claim 159, Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. to produce the RCG fragments which were derived from randomly primer PCR (DOP-PCR) as taught by Cheung et al. and contacting these products to immobilized SNP-ASOs as taught by Saiki et al. with a reasonable expectation of success. The ordinary artisan would have been motivated to modify the method of Shuber et al. to produce the RCG fragments using DOP-PCR (randomly primed PCR derived RCGs) as taught by Cheung et al. because Cheung et al. teaches this method offers a way to amplify small genomic DNA samples to allow hundreds-fold more DNA for genetic analyses (p. 14676 2nd

column 1st paragraph last sentence). The ordinary artisan would be motivated to use the DOP method as taught by Cheung et al. to produce RCGs because Cheung et al. teaches that one can completely cover the entire human genome by breaking up the genome into discrete fragments (Abstract). Cheung et al. further teaches that using the DOP PCR method a small biopsy sample can be used to generate sufficient material for many hundreds of genotyping (p. 146749 1st column last paragraph). Therefore the ordinary artisan would be motivated to produce a large number of RCGs so that many different ASO-probes could be tested in order to diagnose various diseases. The ordinary artisan would be motivated to immobilize the ASO probes taught by Shuber et al. onto a solid support as taught by Saiki et al. because Saiki et al. teaches the preparations of immobilized probes can separate in time their use, allowing for the support to be used to rapidly detect target nucleic acid sequences in test samples on demand (p. 9 lines 24-28). The ordinary artisan would be motivated to have probes immobilized on a support in order to be able to test different samples at different times quickly.

Response to Arguments

The reply traverses the rejection. The arguments made in the response to the nonfinal are summarized below and response to each argument follows.

(A) The reply asserts that the combination of Shuber et al., Cheung et al, and Saiki et al. does not teaches the claimed invention because Shuber et al. does not teach a RCG (reduced complexity genome) (p. 8 last paragraph). The reply asserts that

the instant application defines a RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 9 1st paragraph). The reply asserts that each fragment of the reduced complexity genome has a common sequence at the end (p. 9 1st paragraph). The reply asserts that that the RCG requires less than 20% of the genomic material present in a whole genome (p. 9 first paragraph). The reply asserts Shuber that the fragments of Shuber et al. are present in increased concentration but not fragments of less than 20% of the genomic material (p. 9 1st paragraph). The reply asserts that each fragment in the Shuber et al. method is not a common sequence and therefore is not a RCG as claimed (p. 9 1st paragraph).

This has been fully reviewed but has not been found persuasive. Shuber et al. teaches a method in which genomic DNA is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments". Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Each fragment of the reduced complexity genome would have a common sequence at the end because each fragment would contain a primer sequence at the end which would be considered the common sequence. The claim does not recite rather the "wherein the RCG contains less than 20% of genomic material present in a whole genome" limitation is before the reaction, after the reaction, or a ratio of RCG/genomic DNA at any point. The claim does not clearly recite rather only 20% is amplified or less than 20% is amplified. Since, the cited prior art of Shuber et al., Saiki et al, and Cheung et al. uses a random primer which is

also used by the instant application the percent complexity of the RCG as being less than 20% will be inherently present since all the steps and compositions are the same as the cited combination of references.

(B) The reply asserts that Cheung et al. teaches a method of DOP-PCR which can be used for whole genome amplification (p. 9 2nd paragraph). The reply asserts that therefore Cheung et al would not produce a reduced complexity genome but rather all the genomic material in the whole genome (p. 9 2nd paragraph).

This has been fully reviewed but has not been found persuasive.

Though Cheung et al. teaches that DOP-PCR could be used for whole genome amplification; DOP-PCR is used to produce fragments of the whole genome for genotyping (abstract). Therefore, the DOP-PCR primers used by Cheung et al. makes fragments of the whole genome. The combination of Cheung et al. with Shuber et al. and Saiki et al. therefore would have method steps which produce fragments of the whole genome using DOP-PCR to be used in the later method steps of Shuber et al. to take these fragments and perform hybridization with ASO-probes to detect SNPs and not amplify the whole genome.

10. **Claims 157- 159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) and Cheung et al. (Proceedings National Academy Science 1996 Vol 93 p. 14676) as applied to Claims149-153 and 155-156**

and in view of Hoffman et al. (American Journal of Medical Genetics 1998 Vol. 80 p. 140).

If patentable weight is given to the limitations of "identify a loss of heterozygosity in the tumor" then Claims 157-159 are being rejected over the combination of Shuber et al., Saiki et al., Cheung et al., and Hoffman et al.

With regard to Claim 157, Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which genomic DNA is fragmented by PCR amplification producing RCG (Column 4 lines 10-20). Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30).

With regard to Claim 157, Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification).

With regard to Claim 157, Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification). Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification). Cheung et al. teaches that arbitrary portions of the DNA sequences are amplified by this method (p. 14676 2nd column 1st paragraph). Therefore Cheung et al. teaches preparing a randomly primed PCR-derived reduced complexity genome with at least one primer. Cheung et al. teaches the amplified fragments of DNA

(RCG) are about 500 bp in length (p. 14676 2nd column 1st paragraph); therefore this fragment would contain less than 20% of the genomic material present in the whole genome.

With regard to Claims 158, Cheung et al. teaches that the RCG would be about 500 bp in length (p. 14676 2nd column 1st paragraph). The human genome is about 3 X 10^9 bp in length (p. 14676 2nd column 1st paragraph). Therefore the 500 bp RCG would represent less than 5% of the whole genome.

With regard to Claim 159, Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification).

The combination of Shuber et al., Saiki et al., and Cheung et al. teaches a method of preparing a randomly primer PCR-derived RCG and contacting it with SNP-ASOs to detect the presence or absence of a SNP allele, however, the combination does not teach determining the presence or absence of a SNP allele to identify a loss of heterozygosisty in the tumor.

With regard to Claim 157, Hoffman et al. teaches a method of detecting genetic alterations in DNA in tumor samples (cancer patients) (Abstract). Hoffman et al. teaches a method of using ASO probes to detect a single base change correlated with breast cancer (tumor) (Abstract). Hoffman teaches a plurality of patients had genomic DNA isolated (plurality of RCGs) to detect the SNP ((p. 141 1st column last paragraph and 2nd column ASO hybridization). Hoffman et al. teaches the presence or absence of the SNP allele of each patient and the number of total genomic patient samples (Table 1

and p. 141 last full paragraph), therefore Hoffman et al. teaches the detection of loss of heterozygosity in a tumor.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of detection of SNPs in a RCG using ASO probes as taught by Shuber et al., Cheung et al. and Saiki et al. to detect SNPs in a sample to identify a loss of heterozygosity in the tumor as taught by Hoffman et al. with a reasonable expectation of success. The ordinary artisan would be motivated to modify the method of detection of SNPs in a RCG using ASO probes as taught by Shuber et al., Cheung et al. and Saiki et al. to detect SNPs in a sample to identify a loss of heterozygosity in the tumor as taught by Hoffman et al. because Hoffman et al. teaches that a population can be screened quickly for mutation status to facilitate early diagnosis and treatment by detection of SNPs (p. 140 2nd column 2nd full paragraph). The ordinary artisan would have been motivated to screen a given population for a SNP associated with tumor in order to quickly screen patients for a particular mutation and treat cancer at an earlier stage.

Response to Arguments

The reply traverses the rejection. The reply asserts that the combination of Shuber et al., Saiki et al., and Chueng et al. does not teach a RCG having less than 20% of genomic material present (p. 10 2nd full paragraph). The reply asserts that Hoffman et al. does not provide this missing teaching to the combination (p. 10 2nd full paragraph). This has been fully reviewed but has not been found persuasive.

As discussed above the combination of Shuber et al., Saiki et al., and Chueng et al. provides all the limitations of the independent claim with regard to a RCG having less than 20% genomic material present. The claim does not recite rather the "wherein the RCG contains less than 20% of genomic material present in a whole genome" limitation is before the reaction, after the reaction, or a ratio of RCG/genomic DNA at any point. The claim does not clearly recite rather only 20% is amplified or less than 20% is amplified. Since, the cited prior art of Shuber et al., Saiki et al, and Cheung et al. uses a random primer which is also used by the instant application the percent complexity of the RCG as being less than 20% will be inherently present since all the steps and compositions are the same as the cited combination of references. Hoffman et al. provides the limitation of identifying a loss of heterozygosity in a tumor. Therefore the combination of Shuber et al., Saiki et al, Cheung et al., and Hoffman et al. provides all the limitations of Claims 157-159.

11. **Claims 165 and 166 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Cheung et al. (Proceedings National Academy Science 1996 Vol 93 p. 14676).**

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). With regard to Claim 165, Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification producing RCG (Column 4 lines 10-20). Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30). Shuber et al.

teaches hybridizing the RCG with ASO probes (oligonucleotides) to detect allelic associations (Column 11, lines 25-30).

With regard to claim 166, Shuber et al. teaches a method to determine which individuals has a particular variant sequence (abstract), therefore, Shuber et al. teaches a method to determine a genotype of an individual.

However, Shuber et al. does not teach preparing the PCR amplified RCG using randomly primed PCR.

With regard to Claim 165, Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification). Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification). Cheung et al. teaches that arbitrary portions of the DNA sequences are amplified by this method (p. 14676 2nd column 1st paragraph). Therefore Cheung et al. teaches preparing a randomly primed PCR-derived reduced complexity genome.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of detection of SNPs using ASO-probes as taught by Shuber et al. to produce the RCG fragments using DOP-PCR (randomly primed PCR derived RCGs) as taught by Cheung et al. The ordinary artisan would have been motivated to modify the method of Shuber et al. to produce the RCG fragments using DOP-PCR (randomly primed PCR derived RCGs) as taught by Cheung et al. because Cheung et al. teaches this method offers a way to amplify small genomic DNA samples to allow hundreds-fold more DNA for genetic analyses (p. 14676

2nd column 1st paragraph last sentence). The ordinary artisan would be motivated to use the DOP method as taught by Cheung et al. to produce RCGs because Cheung et al. teaches that one can completely cover the entire human genome by breaking up the genome into discrete fragments (Abstract). Cheung et al. further teaches that using the DOP PCR method a small biopsy sample can be used to generate sufficient material for many hundreds of genotyping (p. 146749 1st column last paragraph). Therefore the ordinary artisan would be motivated to produce a large number of RCGs so that many different ASO-probes could be tested in order to diagnose various diseases, such as tumors, using a small amount of tissue sample.

Response to arguments

The reply traverses the rejection. The reply asserts that the combination of Shuber et al. and Cheung et al. does not teach a reduced complexity genome (p. 11 1st full paragraph). This has been fully reviewed but has not been found persuasive.

Shuber et al. teaches a method in which genomic DNA is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments". Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Cheung et al. teaches using DOP-PCR amplification (randomly primed) to produce genomic fragments (p. 14676 2nd column DOP amplification). Therefore the combination of Shuber et al. and Chueng et al. teach a randomly primed PCR reduced complexity genome.

12. **Claims 149 and 154-156 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989) and in view Drmanac et al. (US Patent 6297006 October 2, 2001).**

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification producing RCG (Column 4 lines 10-20). Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30).

With regard to Claim 149, Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (Column 5 lines 24-25). Shuber et al. teaches a method in which genomic DNA is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 7 paragraph 79 of instant specification). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Shuber et al. teaches a method of detecting the presence or absence of the allele (a SNP) (Column 11 lines 25-30).

Shuber et al. teaches a method incubating RCG (amplified target DNA) with a mixture of allele specific oligonucleotides (ASOs) (Column 4 lines 43-47). Shuber et al.

teaches method of detecting the hybridization of the ASO with the RCG wherein the detection of the hybridization indicates if there is a mutation (characterize the genomic sample) (Column 6 lines 5-10 and column 7 lines 25-35).

Shuber et al. teaches using ASO probes to detect the presence or absence of an allele (abstract). Therefore Shuber et al. teaches using SNP ASOs wherein 50% of the time they are in the RCG (the allele is present).

With regard to Claims 155-156, Shuber et al. teaches a method in which the ASO probes can be from 16-25 nucleotides in length (about 10 to about 50 and about 10 to about 25) (Column 4 lines 49-50).

Shuber et al., however, does not teach immobilization of the SNP-ASO probes onto a surface. Shuber et al. teaches genomic DNA is fragmented by PCR amplification to produce a RCG (Column 4 lines 10-20), but does not teach that the production is by using a randomly primed PCR.

With regard to Claim 149, Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

With regard to Claims 149 and 154, Drmanac et al. teaches a method to reduce a gene or genome into fragments (column 50 lines 58-61). Drmanac et al. teaches producing genomic fragments (RCGs) by digesting a gene with restriction enzymes and performing a PCR with a small set of DNA adapters (adapter primer) (column 50 lines 60-66 and Column 51 1-11). A PCR method would break fragments of DNA into

stretches of nucleotides, which represented least than 20% of the genomic material because each RCG fragment would be only a few KB in size.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. to produce the RCG fragments which were derived from randomly primer PCR (randomly primed PCR derived RCGs) as taught by Drmanac et al. and contacting these products to immobilized SNP-ASOs as taught by Saiki et al. with a reasonable expectation of success. The ordinary artisan would have been motivated to modify the method of Shuber et al. to produce the adapter PCR (randomly primed PCR derived RCGs) as taught by Drmanac et al. because Drmanac et al. Drmanac et al. teaches that by using a small number of adapters a million different fragments may be specifically amplified in identical conditions (Column 51 lines 9-11). The ordinary artisan would be motivated to produce RCGs with adapter PCR, because Drmanac et al teaches that DNA differences between several patients can be analyzed and that this approach eliminates the need for expensive genetic mapping on extensive pedigrees (Column 51 lines 13-23). The ordinary artisan, therefore, would be able to detect genetic differences between subjects quickly and with less cost. The ordinary artisan would be motivated to immobilize the ASO probes taught by Shuber et al. onto a solid support as taught by Saiki et al. because Saiki et al. teaches the preparations of immobilized probes can separate in time their use, allowing for the support to be used to rapidly detect target nucleic acid sequences in test samples on demand (p. 9 lines 24-28). The ordinary artisan would be

motivated to have probes immobilized on a support in order to be able to test different samples at different times quickly.

Response to Arguments

The reply traverses the rejection. The arguments made in the response to the nonfinal are summarized below and response to each argument follows.

(A) The reply asserts that the combination of Shuber et al., Saiki et al., and Drmanac et al. does not teach a reduced complexity genome (p. 11 4th full paragraph). The reply asserts that the teachings of Drmanac et al. pertains to the sequencing of fragments (p. 11 last paragraph). The reply asserts that the fragments of Drmanac et al. is not a reproducible fraction of the isolated genome but merely the isolation of a limited number of genes (p. 12 1st paragraph).

This argument has been fully reviewed but has not been found persuasive.

The reply asserts that the combination of Shuber et al., Drmanac et al, and Saiki et al. does not teaches the claimed invention because Shuber et al. does not teach a RCG (reduced complexity genome) (p. 8 last paragraph). Shuber et al. teaches a method in which genomic DNA is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments". Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Each fragment of the reduced complexity genome would have a common sequence at the end because each fragment would contain a primer sequence at the end which

would be considered the common sequence. The claim does not recite rather the "wherein the RCG contains less than 20% of genomic material present in a whole genome" limitation is before the reaction, after the reaction, or a ratio of RCG/genomic DNA at any point. The claim does not clearly recite rather only 20% is amplified or less than 20% is amplified. Since, the cited prior art of Shuber et al., Saiki et al, and Drmanac et al et al. uses a random primer which is also used by the instant application the percent complexity of the RCG as being less than 20% will be inherently present since all the steps and compositions are the same as the cited combination of references.

(B) The reply asserts that the ordinary artisan would not have combined the teachings of Shuber et al. and Drmanac et al. (p. 12 2nd paragraph). The reply asserts that Drmanac et al. teaches using a small number of adapters a million different fragments may be specifically amplified in identical conditions whereas a PCR would not be used to amplify a million different fragments (p. 12 point 1). The reply asserts that Drmanac seeks to avoid the need for expensive genetic mapping on extensive pedigrees by sequencing and therefore would not have used the method for generation of the ASOs used in the hybridization step of Shuber et al. (p. 12 point 2).

These arguments have been fully reviewed but have not been found persuasive.

Though Drmanac et al. teaches a million different fragments may be amplified in identical conditions, it does not, however imply that all of these fragments are produced at the same time. Drmanac et al. merely teaches the use of adapter primers in a PCR

method which would be the same primer type as Claim 154. It would be obvious to modify the method of Shuber et al. to incorporate adapter primers into the method step of PCR in order to amplify fragments in identical conditions. Though Drmanac et al. further teaches method steps for sequencing, the step which would be combinable with Shuber et al. is the step of adding adapter primers to a PCR solution. In this incorporation the teachings of Drmanac et al. allow the PCR to be produced with adapter primers such that fragments can be analyzed using the ASO probes of Shuber et al.

13. **Claims 157 and 160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Saiki et al. (WO 89/11548 November 30, 1989), Drmanac et al. (US Patent 6297006 October 2, 2001), and in view of Hoffman et al. (American Journal of Medical Genetics 1998 Vol. 80 p. 140).**

With regard to Claim 157, Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which genomic DNA (native DNA) is fragmented by PCR amplification producing RCG (Column 4 lines 10-20). Shuber et al. teaches a method of detecting the presence or absence of the allele using ASO probes (Column 11 lines 25-30).

Shuber et al. teaches a method for detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (Column 5 lines 24-25). Shuber et al. teaches a method in which

genomic DNA is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 7 paragraph 79 of instant specification). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Shuber et al. teaches a method of detecting the presence or absence of the allele (a SNP) (Column 11 lines 25-30).

Shuber et al. teaches a method incubating RCG (amplified target DNA) with a mixture of allele specific oligonucleotides (ASOs) (Column 4 lines 43-47). Shuber et al. teaches method of detecting the hybridization of the ASO with the RCG wherein the detection of the hybridization indicates if there is a mutation (characterize the genomic sample) (Column 6 lines 5-10 and column 7 lines 25-35).

Shuber et al. teaches using ASO probes to detect the presence or absence of an allele (abstract). Therefore Shuber et al. teaches using SNP ASOs wherein 50% of the time they are in the RCG (the allele is present).

Shuber et al., however, does not teach immobilization of the SNP-ASO probes onto a surface. Shuber et al. teaches genomic DNA is fragmented by PCR amplification to produce a RCG (Column 4 lines 10-20), but does not teach that the production is by using a randomly primed PCR. Shuber et al. does not teach detecting the presence or absence of a SNP allele to identify a loss of heterozygosity in a tumor.

With regard to Claim 157, Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (Abstract).

With regard to Claims 157 and 160, Drmanac et al. teaches a method to reduce a gene or genome into fragments (column 50 lines 58-61). Drmanac et al. teaches producing genomic fragments (RCGs) by digesting a gene with restriction enzymes and performing a PCR with a small set of DNA adapters (adapter primer) (column 50 lines 60-66 and Column 51 1-11). A PCR method would break fragments of DNA into stretches of nucleotides, which represented least than 20% of the genomic material because each RCG fragment would be only a few KB in size.

With regard to Claim 157, Hoffman et al. teaches a method of detecting genetic alterations in DNA in tumor samples (cancer patients) (Abstract). Hoffman et al. teaches a method of using ASO probes to detect a single base change correlated with breast cancer (tumor) (Abstract). Hoffman teaches a plurality of patients had genomic DNA isolated (plurality of RCGs) to detect the SNP ((p. 141 1st column last paragraph and 2nd column ASO hybridization). Hoffman et al. teaches the presence or absence of the SNP allele of each patient and the number of total genomic patient samples (Table 1 and p. 141 last full paragraph), therefore Hoffman et al. teaches the detection of loss of heterozygosity in a tumor.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber et al. to produce the RCG fragments which were derived from randomly primer PCR (randomly primed PCR derived RCGs) as taught by Drmanac et al. and contacting these products to immobilized SNP-ASOs as taught by Saiki et al. to identify a loss of heterozygosity in a tumor as taught by Hoffman et al. with a reasonable expectation of success. The

ordinary artisan would have been motivated to modify the method of Shuber et al. to produce the adapter PCR (randomly primed PCR derived RCGs) as taught by Drmanac et al. because Drmanac et al. Drmanac et al. teaches that by using a small number of adapters a million different fragments may be specifically amplified in identical conditions (Column 51 lines 9-11). The ordinary artisan would be motivated to produce RCGs with adapter PCR, because Drmanac et al teaches that DNA differences between several patients can be analyzed and that this approach eliminates the need for expensive genetic mapping on extensive pedigrees (Column 51 lines 13-23). The ordinary artisan, therefore, would be able to detect genetic differences between subjects quickly and with less cost. The ordinary artisan would be motivated to immobilize the ASO probes taught by Shuber et al. onto a solid support as taught by Saiki et al. because Saiki et al. teaches the preparations of immobilized probes can separate in time their use, allowing for the support to be used to rapidly detect target nucleic acid sequences in test samples on demand (p. 9 lines 24-28). The ordinary artisan would be motivated to have probes immobilized on a support in order to be able to test different samples at different times quickly. The ordinary artisan would be motivated to modify the method of detection of SNPs in a RCG using ASO probes as taught by Shuber et al to detect SNPs in a sample to identify a loss of heterozygosity in the tumor as taught by Hoffman et al. because Hoffman et al. teaches that a population can be screened quickly for mutation status to facilitate early diagnosis and treatment by detection of SNPs (p. 140 2nd column 2nd full paragraph). The ordinary artisan would have been

motivated to screen a given population for a SNP associated with tumor in order to quickly screen patients for a particular mutation and treat cancer at an earlier stage.

Response to Arguments

The reply traverses the rejection. The reply asserts that the combination of Shuber et al., Saiki et al, Hoffman et al., and Drmanac et al. does not teach RCGs (p. 13 3rd paragraph).

This argument has been fully considered but has not been found persuasive.

The reply asserts that the combination of Shuber et al., Drmanac et al, and Saiki et al. does not teaches the claimed invention because Shuber et al. does not teach a RCG (reduced complexity genome) (p. 8 last paragraph). Shuber et al. teaches a method in which genomic DNA is fragmented by PCR amplification (Column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments". Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition. Each fragment of the reduced complexity genome would have a common sequence at the end because each fragment would contain a primer sequence at the end which would be considered the common sequence. The claim does not recite rather the "wherein the RCG contains less than 20% of genomic material present in a whole genome" limitation is before the reaction, after the reaction, or a ratio of RCG/genomic DNA at any point. The claim does not clearly recite rather only 20% is amplified or less than 20% is amplified. Since, the cited prior art of Shuber et al., Saiki et al, and

Drmanac et al et al. uses a random primer which is also used by the instant application the percent complexity of the RCG as being less than 20% will be inherently present since all the steps and compositions are the same as the cited combination of references.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 149-160, 165-166 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6703228. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant Claim 149 contain the same method steps as Claims 1-2 and 4 of Patent No. 6703228 (herein called '228), except the instant Claim requires that the RCG contains less than 20% of genomic material present and a loci corresponding to the SNP-ASO present with a frequency of at least 50% in the RCG.

Claims 39-40 of the '228 patent requires a reduced complexity of 95% or 99%. Therefore the RCG will contain less than 20% of the genomic material present.

Claim 25 of the '228 patent requires detect the presence or absence of an allele. Therefore the claim requires using SNP ASOs wherein 50% of the time they are in the RCG (frequency is at least 50%).

Therefore Claims 1-2, 4, 39-40, and 25 of the '228 contain all the limitations of the instant applications Claim 149.

Claims 150-152 are obvious over Claims 39-40 of the '228 patent.

Claims 153 of the instant application is obvious over Claim 29 of the '228 patent.

Claim 154 of the instant application is obvious over claim 33 of the '228 patent.

Claim 155-156 of the instant application is obvious over claims 20-21 of the '228 patent.

Claim 157 of the instant application is obvious over the combination of the limitations of Claims 1-2, 4, 25, and 39-40 of the '228 patent and claim 27 of the '228 patent wherein the sample is obtained from a tumor.

Claims 158 is obvious over Claims 39-40 of the '228 patent.

Claims 159 of the instant application is obvious over Claim 29 of the '228 patent.

Claim 160 of the instant application is obvious over claim 33 of the '228 patent.

Claims 165-166 contain the same method steps as the combination of the limitations of Claims 1-2, 4, 25, and 39-40 of the '228 patent.

Response to Arguments

It is noted that the rejection of claims 149-160 is newly applied. With regard to the double patenting rejection made of record for Claims 165-166 made of record in the prior nonfinal rejection (1/29/2007) and the pending rejection for claims 149-160 and 165-166, applicant defers any rebuttal of the rejection until it is the last remaining rejection (p. 14 1st and 2nd paragraph).

Conclusion

14. No Claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER